REMARKS

Upon entry of this amendment, claims 57 to 102 will be pending in the application.

Please cancel claims 4-15, 18-23, 39, 40, 42- 47 and 49-56, without prejudice to all disclaimer.

The newly presented claims 67 to 102 are fully supported by the previously pending claims. The new claims are being presented to allow easier examination because the previous claims listed dependent claims before independent claims, which was confusing.

In rewriting the claims, cosmetic changes were also made to some of the claims, to clarify or render claim language more consistent. These amendments only made express, recitation of features which were already present in the original claims, and thus, are not a narrowing of the scope of the properly construed claim. TurboCare v. General Electric Co., 264 F.3d 1111 (Fed. Cir. 2001); Bose Corp. v. JBL, Inc., 274 F.3d 1354 (Fed. Cir. 2001); and Interactive Pictures Corp. v. Infinite Pictures, Inc., 274 F.3d 1371 (Fed. Cir. 2001). Thus the scope of the doctrine of equivalents applied to the claims should not be limited under the rules of Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., 535 U.S. 722, 2002 Lexis 3818 (May 28, 2002).

Rejection Under 35 U.S.C. § 103(a)

1. The Examiner rejected original claims 4-15, 18-23, 39-47, 49-50 and 55-56 under 35 U.S.C. § 103(a) as unpatentable over Hanes et al. (US 5,855,913) in view of Unger (6,120,751).

The present claims are not obvious over Hanes et al. in view of Unger. To establish obviousness, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). In determining the differences between the prior art and the claims, the question under 35 USC 103 is not whether the differences themselves would have been obvious, but whether the claimed invention as a whole would have been obvious. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F. 2d 1530, 218 USPQ 871 (Fed. Cir. 1983). In determining obviousness, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Added claim 57 (which is based on canceled independent claim 39) claims an inhaleable powder composition comprising a plurality of particulate microstructures, the microstructures comprising a structural matrix composed of phospholipid and calcium, an active agent, a mean geometric diameter of 1-30 microns, a mean aerodynamic diameter of less than 5 microns, and a bulk density of less than about 0.5 g/cm^3.

Added claim 80 further recites that the particulate microstructures comprise a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C.

The combination of Hanes et al. and Unger do not teach or suggest the inhalable composition of claim 57 or claim 80, when the composition recited in these claims is considered as a whole.

The Examiner cites Hanes et al. to teach aerodynamic particles having various desirable properties such as aerodynamic diameter, mass median diameter, tap density, etc..

However, while Hanes et al. teaches desirable aerodynamic properties for inhalable particles, Hanes et al. does not teach or suggest the particulate microstructure being claimed, namely a particulate microstructure comprising a structural matrix composed of phospholipid and calcium.

Instead, Hanes et al. teaches aerodynamic particles made from inorganic and organic materials, such as ceramic or polymer. (Column 5, line 47 to column 6, line 59). Hanes also teaches a providing a surfactant, such as DPPC, on the surfaces of these ceramic/polymer particles to reduce the tendency of the particles to agglomerate due to electrostatic interactions. Hanes teaches that particle aggregation is a problem and this aggregation can be reduced by the use of surfactants:

> ...An effective dry-powder inhalation therapy for both short and long-term release of therapeutics, either for local or systemic delivery, requires a powder that displays minimum aggregation, as well as a means of avoiding or suspending the lung's natural clearance mechanisms until drugs have been effectively delivered.
>
> (Column 3, lines 27-32).

Hanes et al., further teaches a surfactant to be an agent which preferentially absorbs to an interface between two phases:

> As used herein, the term "surfactant" refers to any agent which preferentially absorbs to an interface between two immiscible phases, such as the interface between water and an organic polymer solution, a water/air interface or organic solvent/air interface.
>
> (Column 5, lines 5-9).

Hanes et al. also teaches that "[p]roviding a surfactant on the surfaces of the particles can reduce tendency of the particles to agglomerate due to interactions such as electrostatic interactions." (Column 5, lines 27-29). Hanes et al. then teaches that the surfactant can

be applied on particles that include both inorganic and organic materials, such as ceramics and polymers. (Column 5, line 47 to column 6, line 59). Thus, Hanes et al. does not teach particulate microstructures comprising a structural matrix composed of phospholipid, as claimed.

Hanes et al. briefly mentions, in the passing, that a particle can be made from a surfactant. However, particles made entirely from a surfactant are not enabled by Hanes et al. and it is clearly evident from each and every one of the examples that Hanes et al. teaches only how to make particles from polymers. For example, Example 1 teaches formation of particles from poly[(p-carboxyphenoxy)-hexane anhydride] also known as "PCPH". Example 2 teaches the formation of spray dried particles from PLGA. Example 3 teaches fabrication of a particle from PLGA, and to which DPPC (phospholipid) was added as a lung surfactant to improve its surface properties. Example 4 teaches fabrication of a particle from PLGA with a DPPC surfactant coating, which is not a particle having a structural matrix of phospholipid. Thus, as demonstrated, Hanes et al. also does not teach particulate microstructures comprising a structural matrix of phospholipid.

Further, as acknowledged by the Examiner, Hanes et al. does not teach the use of calcium in particulate microstructures comprising a structural matrix of phospholipid. The Examiner further cites Unger to teach the addition of calcium to the particulate microstructures taught by Hanes et al..

However, Unger should not be combined with Hanes et al. to derive the claimed particulate microstructures because Hanes et al. and Unger both teach different types of particles than those being claimed. As explained above, Hanes et al. teaches particles made from polymer. Unger teaches particles that have to include a lipid which is covalently bonded to a polymer. Unger teaches: "[t]he present invention describes compositions which comprise one or more charged lipids, counter ions and at least one lipid which is covalently bonded to a polymer." (Column 9, line 66 to column 10, line 1).

Unger further teaches the importance of the lipid comprising a polymer, namely:

> The lipid covalently bonded to the polymer stabilizes the compositions so that they form well-defined vesicles. If the lipid covalently bonded to the polymer is not used in the compositions of the present invention, the counter ions cause the charged lipids species to form amorphous lipid clumps. In many cases, the lipid clumps may take the form of, for example, condensed lipid bilayers, but the lipid clumps do not form stable vesicles with size distributions suitable, for example, or intravenous injection.

(Column 10, lines 41-49). Thus Unger teaches a particle fabricated using a least one lipid which is covalently bonded to a polymer. Further, Unger teaches that the lipid covalently bonded to the polymer is essential to form a stable vesicle structure. In contrast, the present claims are to a particles having a structural matrix comprising a phospholipid, and not a lipid covalently bonded to a polymer.

Unger further teaches that the calcium added to the structure provides unique benefits in relation to the lipid covalently bonded to the polymer. Specifically, Unger teaches "[t]he lipid covalently bonded to a polymer (e.g., DPPE-PEG-5,000) causes compaction of the size of the composition in the presence of a counter ion, such as Ca^{2+}...". Thus, Unger teaches that the lipid covalently bonded to the polymer undergoes a transformation in the presence of the calcium ion. Unger also teaches that:

> Increasing the amount of the lipid covalently bonded to a polymer allows the composition to stabilize at sizes generally under about 1.0 μm in the presence of a counter ion. When the lipid covalently bonded to the polymer is present in an amount less than about 5%, the composition is generally unstable and may precipitate.

(Column 10, lines 61-66.) Thus, the particle taught by Unger requires the presence of a lipid covalently bonded to a polymer, and further, the calcium addition taught by Unger, results in a unique structure for lipids covalently bonded to the polymer. Thus, neither Unger nor Hanes et al. teach or suggest the benefits of adding calcium to a particulate microstructure having a structural matrix of phospholipid.

Furthermore, there is no motivation to add the calcium ion taught by Unger to the particles taught by Hanes et al. to derive discrete particulate microstructures that exhibit decreased aggregation, as claimed. Unger et al. teaches that the addition of calcium can result in particulate aggregation. In relation to the teachings of Unger, the Office Action states Applicant "has misconstrued Unger's use of the term 'aggregate'." Applicant respectfully disagrees. The Office Action cites Unger to teach at column 10:

> ... the counter ions (calcium) form salt bridges which crosslink the charged lipids to form aggregates **or** multilamellar vesicles. The aggregates **or** multilamellar vesicles may be referred to cochleates, which may be in the form of a tubule or a spiral. [Emphasis added.]

Applicant submits that the use of the alternative language "or" suggests that Unger teaches that the counter ions form bridging structures that can certainly form aggregates – which is undesirable for inhalable compositions because aggregated particles would not have the necessary aerodynamic properties for penetrating deep into the lung. Furthermore, Unger teaches:

> Studies have described the effects of calcium and other multivalent cations on membrane asymmetry, lipid distribution, vesicle size, aggregation and fusion. Although the underlying physical causes for the phenomena are debatable, general consensus exists that multivalent cations, such as calcium and magnesium, in the external environment of phospholipid vesicles cause the structures to **aggregate** into larger, multilamellar structures and promotes fusion. ...
>
> ... The effects of calcium-induced aggregation are so pronounced that efforts have been undertaken to limit the effect in order to control the size of liposomes used in drug delivery systems by forming vesicles in which calcium ions are confined to outer surfaces of the bilayer. ...

[Emphasis added]. (Unger, column 1, line 50 to column 2, line 9.) Thus, Unger teaches that calcium in the external environment of already formed phospholipid vesicles. Unger also teaches "[a] vesicle refers to an entity which is generally characterized by the presence of one or more walls or membranes which form one or more internal voids." (Column 4, lines 18-21). Thus the vesicles appear to be enclosed structures with internal

voice, and Unger teaches that these vesicle structures aggregate together with the addition of calcium. Such an aggregation would teach away from the claimed inhaleable powder composition comprising a plurality of discrete particulate microstructures which exhibit reduced aggregation, as claimed. Thus, Unger does not motivate addition of calcium to the particulate structures taught by Hanes et al. to form discrete, non-aggregated structures, but instead teaches that aggregation of enclosed vesicles results from the addition of calcium to vesicle structures.

As taught in the present application, aggregation of particulate microstructures is undesirable as it reduces the dispersibility of the powder composition, which in turn affects how far the particulate structures travel into the pulmonary system. For example, the present Specification teaches:

> In order to maximize dispersibility, dispersion stability and optimize distribution upon administration, the mean geometric particle size of the perforated microstructures is preferably about 0.5-50 μm, more preferably 1-30 μm. It will be appreciated that large particles (i.e. greater than 50 μm) may not be preferred in applications where a valve or small orifice is employed, since large particles tend to aggregate or separate from a suspension which could potentially clog the device.

(Specification, page 32, lines 11-16.)

> With respect to the advantageous deposition profile provided by the instant invention it is well known that MDI propellants typically force suspended particles out of the device at a high velocity towards the back of the throat. Since prior art formulations typically contain a significant percentage of large particles and/or aggregates, as much as two-thirds or more of the emitted dose may impact the throat.

(Specification, page 39, lines 24-28.) Thus, the Specification teaches that aggregated particles are undesirable because they tend to separate from a suspension and clog the inhaler device. Also, as explained, prior art formulations such as those taught by Unger contain aggregates which result in a large percentage, as much as two-thirds or more of

the emitted dose, impacting the throat and not traveling deep into the lungs, which is undesirable in inhalation therapy.

Unger also does not make up for the deficiencies of Hanes, because Unger also does not teach particulate microstructures having the aerodynamic properties of the claimed particulate microstructures having a structural matrix of phospholipid. Specifically, Unger does not teach particles suitable for an inhalable composition, and which have a mean aerodynamic diameter of less than 5 microns, a mean geometric diameter of 1-30 microns, and a bulk density of less than about 0.5 g/cm^3.

Thus, when considered as a whole, the Hanes et al. and Unger references do not teach the claimed inhaleable powder composition because the cited references do not teach or suggest, or motivate derivation of, the application of calcium aerodynamic particles comprising a structural matrix of phospholipid. "In making the assessment of differences between the prior art and the claimed subject matter, section 103 specifically requires consideration of the claimed invention 'as a whole.'" Princeton Biochemicals, Inc. v. Beckman Coulter, Inc. (Fed. Cir., No. 04-1493, 6/9/05). "[S]imply identifying all of the elements in a claim in the prior art does not render a claim obvious. Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1275 (Fed. Cir. 2004). Hanes et al. makes no mention of calcium, teaches that particle aggregation is a problem, and further teaches the use of surfactants to reduce particle agglomeration. Unger teaches that calcium addition results in the aggregation of vesicles, and also teaches calcium addition to lipids comprising a covalently bonded polymer, and not a particle comprising a structural matrix of phospholipid as claimed.

Further, there is no reasonable expectation of success that the cited combination of references would operate as suggested by the Examiner. Specifically, Hanes et al. teaches that an organic solvent dissolved polymer is suspended in an aqueous medium containing a surface active agent, such as PVA, to form an emulsion that is stirred until the organic solvent evaporates to leave behind polymer particles. If the particles made by this method were further aggregated with the addition of calcium to the

aqueous medium, the resultant composition would have large aggregated particles which may well have particle sizes larger than those described by Hanes et al.. In fact, Hanes et al. teaches the use of surfactants to reduce particle agglomeration, which further evidences that Hanes et al. teaches against the use of a calcium aggregating agent as taught by Unger, and evidences the lack of motivation for this combination of references.

For these reasons, the combination of Hanes et al. and Unger do not provide sustain the obviousness rejection. Hanes et al. teaches polymer or ceramic particles, and Unger teaches particles made from a lipid covalently bonded to a polymer. Hanes et al. does not teach the addition of calcium. Unger et al. teaches addition of calcium to the lipid covalently bonded to a polymer, and not a particulate microstructure comprising a structural matrix of phospholipid. Further the reasons for which Unger motivates application of calcium to a composition comprising a lipid covalently bonded to a polymer, do not apply to the present particles which do not recite a lipid covalently bonded to a polymer. Unger also does not teach aerodynamic particles on the desirable properties. Thus neither reference teaches or suggests, or motivates derivation of an aerodynamic particle comprising a structural matrix of phospholipid with calcium, as claimed.

Thus claims 57 and 80 and their dependent claims are not rendered unpatentable by Hanes et al. in view of Unger. Accordingly, the Examiner is respectfully requested to allow the present claims.

Rejection Under 35 U.S.C. § 103(a) of Claims 51-52

The Examiner rejected claims 51-52 as being unpatentable over Hanes et al. in view of Unger and further view of Igarashi (4,201,774). This rejection is also respectfully traversed.

Previously pending claims 51 and 52 correspond to newly added claims 78 and 101, and these claims are to an inhalable powder composition in which bioactive agent is an aminoglycoside antibiotic.

As acknowledged by the Examiner, Hanes et al. does not teach an aminoglycoside antibiotic. Neither reference teaches a particulate microstructure comprising a structural matrix comprising phospholipid and calcium. Instead, Hanes et al. teaches polymer or ceramic particles while Unger teaches particles that include a lipid covalently bonded to a polymer. Further, Hanes et al. does not teach the addition of calcium. Unger et al. teaches addition of calcium to the lipid covalently bonded to a polymer, and thus, only motivates application of calcium to a composition comprising a lipid covalently bonded to a polymer. Unger also does not teach aerodynamic particles on the desirable properties. Thus neither reference teaches or suggests, or motivates derivation of an aerodynamic particle comprising a structural matrix of phospholipid with calcium, as claimed. The Igarashi reference also does not teach or suggest particulate microstructures comprising phospholipid, calcium and an active agent, as claimed. Thus Hanes et al., Unger and Igarashi, do teach or suggest the claimed powder composition comprising particulate microstructures comprising phospholipid, calcium and an active agent, as recited in claims 57 and 80.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to include a phospholipid having a gel to liquid crystal transition temperature of greater than 40°C, as claimed in claim 80. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, Applicant respectfully submits that claims 78 and 101 are allowable over the cited references.

Rejection Under 35 U.S.C. § 103(a) of Claims 53-54

The Examiner rejected claims 53-54 as being unpatentable over Hanes et al in view of Unger and in further view of Benson et al (5,006,343). This rejection is also respectfully traversed.

Previously pending claims 53 and 54 correspond to newly added claims 79 and 102, which are to an inhaleable powder composition that includes a bioactive agent that is a fungicide.

Hanes et al. does not teach a particulate microstructure comprising a structural matrix comprising phospholipid and calcium. Instead, Hanes et al. teaches polymer or ceramic particles. Hanes et al. also does not teach the addition of calcium. The Examiner also acknowledges than Hanes et al. does not teach the use of calcium to stabilize the phospholipids, and that Hanes et al. also does not teach the specific use of fungicides.

Unger et al. teaches addition of calcium to the lipid covalently bonded to a polymer, and thus, only motivates application of calcium to particles comprising a lipid covalently bonded to a polymer. Unger also does not teach aerodynamic particles on the desirable properties.

Thus neither Hanes et al. or Unger reference teaches or suggests, or motivates derivation of an aerodynamic particle comprising a structural matrix of phospholipid with calcium, as claimed. Benson also does not teach or suggest a particulate microstructure comprising phospholipid, calcium and an active agent. Instead the Examiner cites Benson only for teaching a fungicide. Thus, Hanes et al., Unger and Benson do not teach or suggest a powder composition comprising discrete particulate microstructures comprising phospholipid, calcium and an active agent.

Furthermore, Hanes et al., Unger or Igarashi do not teach or suggest that it is desirable to have particulate microstructures that include phospholipid having a gel to

liquid crystal transition temperature of greater than 40°C, as claimed in claim 80. Nor is this teaching to a particular temperature range obvious to one of ordinary skill, simply from a teaching that phospholipids are desirable to form particulate microstructures.

For these reasons, the Examiner respectfully requested to allow claims 79 and 102 over the cited references.

Provisional Double Patenting Rejections

The provisional double patenting rejections will be addressed by the filing of one or more Terminal Disclaimers upon indication of allowable subject matter in the present application, since the double patenting rejection is provisional.

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

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